TV-121-120120-65

SYLLABUS AND COURSE GUIDE

The Role of Antibody Drug Conjugates in Advanced Non-Small Cell Lung Cancer: Guidance for Today and the Path Forward

A Free, 90-Minute Live and OnDemand Activity
Premiere Date: Tuesday, December 1, 2020
12:30 PM - 2:00 PM ET (live)
Credit Expiration Date: Wednesday, December 1, 2021

www.cmeoutfitters.com/NSCLCguidance
#NSCLCcare

LIVE FACULTY:
Hossein Borghaei, DO, MS (Moderator)
Enriqueta Felip, MD, PhD
David E. Gerber, MD

Take advantage of our LIVE Q&A segment during this webcast!

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INFORMATION FOR PARTICIPANTS

Statement of Need

The discovery of molecular alterations that drive tumor initiation and progression has revolutionized the treatment strategy for non-small cell lung cancer (NSCLC) by matching targeted therapies to a specific mutation, leading to significantly improved therapeutic efficacy. However, despite the initial effectiveness of targeted therapy for NSCLC, most patients ultimately develop acquired resistance with subsequent disease progression, making it imperative for clinicians to receive up-to-date education on evaluating new therapeutic options to improve outcomes and better tailor treatment strategies.

In this CME Outfitters Live and OnDemand, integrations of animated 3-D models will provide visual representation of the mechanisms and characteristics of antibody drug conjugates (ADCs) in NSCLC to complement expert faculty insights and evidence supporting testing strategies to identify predictive biomarkers, emerging treatment options for advanced or metastatic NSCLC, and best practices for managing patients with lung cancer in the face of COVID-19 and beyond.

Learning Objectives

At the end of this CME/CE activity, participants should be able to:

- Apply molecular testing to identify predictive biomarkers for targeted therapy in advanced NSCLC.
- Evaluate the rationale for emerging therapies in advanced or metastatic NSCLC.
- Employ best practices to manage lung cancer during the COVID-19 pandemic.

The following learning objectives pertain only to those requesting CNE or CPE credit:

- Summarize how molecular testing can identify predictive biomarkers for targeted therapy in advanced NSCLC.
- Evaluate the rationale for emerging therapies in advanced or metastatic NSCLC.
- Describe best practices to manage lung cancer during the COVID-19 pandemic.

Target Audience

Hematology/oncology specialists, surgeons, pathologists, nurse practitioners, PAs, nurses, and pharmacists

Financial Support

Supported by an educational grant from Daiichi Sankyo, Inc.

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Universal Activity Number: Live: 0376-0000-20-148-L01-P; Enduring: 0376-0000-20-148-H01-P
Type: Knowledge-based

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Learning Formats: Live activity; Enduring material

Royal College MOC

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MIPS Improvement Activity

This activity counts towards MIPS Improvement Activity requirements under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Clinicians should submit their improvement activities by attestation via the CMS Quality Payment Program website.

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There is no fee for participation in this activity. The estimated time for completion is 90 minutes. Questions? Please call **877.CME.PROS**.

FACULTY BIOS & DISCLOSURES

Hossein Borghaei, DO, MS (Moderator)

Dr. Borghaei earned his degree at Philadelphia College of Osteopathic Medicine and completed a residency at Graduate Hospital in Philadelphia. Since completing his fellowship training at Fox Chase Cancer Center, he has been involved in a number of clinical trials aimed at developing new, antibody-based therapies and immunotherapies for patients with lung cancer.

In addition to his clinical practice and participation in immunotherapy-based clinical trials, Dr. Borghaei is the principal investigator (PI) of a laboratory that develops new monoclonal antibodies and novel immune-modulating drugs, with the aim of bringing these approaches to the clinic. He served as the PI of a phase III randomized study that proved the effectiveness of nivolumab in the treatment of patients with advanced non-squamous non-small cell lung cancer after progression on prior chemotherapy. This work led to the approval of nivolumab, one of the first immunotherapy-based drugs to be approved for lung cancer in this setting.

Dr. Borghaei is a member of the thoracic core committee at Eastern Cooperative Oncology Group (ECOG) and, until recently, was a member of the National Comprehensive Cancer Network (NCCN) Non-Small Cell Lung Cancer panel. He is the recipient of an American Society of Clinical Oncology (ASCO) Young Investigator Award and an ASCO Career Development Award. Dr. Borghaei is a long-standing member of ASCO, AACR, IASLC, and SITC as well as the ECOG thoracic committee.

Dr. Borghaei has been a recipient of the Robert Krigel Memorial Award for Teaching Excellence from Fox Chase Cancer Center, ASCO's Young Investigator Award, and the Career Development Award from ASCO. His work has been published in *The New England Journal of Medicine, Journal of Clinical Oncology, The Lancet Oncology, Leukemia Research, Journal of Thoracic Oncology, Clinical Cancer Research, Clinical Lung Cancer,* and *Journal of the National Comprehensive Cancer Network*.

Enriqueta Felip, MD, PhD

Dr. Felip is the Head of the Thoracic Cancer Unit within the Oncology Department of Vall d'Hebron Hospital, Barcelona, Spain. Professor Felip is in charge of thoracic malignancy management and is responsible for thoracic cancer trials undertaken by the Oncology Department. Dr. Felip received her medical degree from the Autonomous University of Barcelona (UAB), where she also completed her PhD studies in medical oncology. She has been Associate Professor at UAB from 2010 to May 2019. She is involved in the training of medical students, residents, and particularly in mentoring fellows.

Dr. Felip is currently a member of the Spanish Lung Cancer Group (SLCG) and the Spanish Society of Medical Oncology (SEOM). In October 2019, she was elected SEOM Vice-President for 2019-2021.

Dr. Felip is also member of the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the International Association for the Study of Lung Cancer (IASLC). She is a member of the Board of Directors of IASLC (2017-2021).

Dr. Felip has been involved in several initiatives with scientific organizations, among them, as Subject Editor of Guidelines Working group ESMO Minimum Clinical Recommendations in lung cancer and Coordinator of the 1st ESMO Consensus Conference in lung cancer. She is at present a member of the scientific committee of the SLCG.

Dr. Felip is also author of many peer-reviewed articles and book chapters relating to the field of thoracic malignancies.

The magnitude of Dr. Felip's contribution to the biomedical sciences is remarkable as she is one of the most cited authors in 2018 and 2019: Global Highly Cited Researcher list 2018 (Source: Clarivate Analytics).

David E. Gerber, MD

Dr. Gerber is Professor of Internal Medicine and Population & Data Sciences at UT Southwestern Medical Center. Within the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern, Dr. Gerber serves as Associate Director of Clinical Research and as Co-Leader of the Experimental Therapeutics Scientific Program.

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Dr. Borghaei reports he receives research support from Bristol-Myers Squibb Company/Eli Lilly and Company and Merck & Co./Celgene Corporation. He is on the advisory committee for AbbVie Inc.; Amgen Inc.; AstraZeneca; Axiom Healthcare Services; BioNTech; Boehringer Ingelheim; Bristol-Myers Squibb Company; Cantargia AB; Celgene Corporation; Daiichi Sankyo, Inc.; Eli Lilly and Company; EMD Serono, Inc.; Genentech, Inc.; Genmab; GLG; HUYA Bioscience International; Merck & Co.; Novartis; Pfizer Inc.; PharmaMar; Regeneron Pharmaceuticals Inc.; and Takeda Pharmaceuticals U.S.A., Inc. He is a consultant for Amgen; AstraZeneca; Bristol-Myers Squibb Company; Daiichi Sankyo, Inc.; EMD Serono, Inc.; and PharmaMar. He receives other financial or material support from Data and Safety Monitoring Board: Incyte; Takeda Pharmaceuticals U.S.A., Inc. and University of Pennsylvania. He is on the scientific advisory board for Rgenix (stock options) and Sonnet BioTherapeutics, Inc. (stock options).

Dr. Felip reports she receives research funding from Fundación Merck Salud and a grant for Oncology Innovation (GOI) EMD Serono. She serves in an advisory role or speakers bureau for for AbbVie Inc.; Amgen Inc.; Astra Zeneca, Bayer, Blueprint Medicines Corporation; Boehringer Ingelheim; Bristol-Myers Squibb Company; Eli Lilly and Company; F. Hoffmann-La Roche; GlaxoSmithKline; Janssen Global Services; Merck KGaA; Merck Sharp & Dohme Corp.; Novartis; Pfizer Inc.: Puma Biotechnology, Inc.; Sanofi Genzyme, Springer; and Takeda Pharmaceutical Company. She recieves other financial or material support from Grifols (independent board member).

Dr. Geber reports he receives research support from AstraZeneca; BerGenBio; Bristol-Myers Squibb Company; and Karyopharm. He is a consultant for Bristol-Myers Squibb Company; Catalyst Pharmaceuticals, Inc.; G1 Therapeutics, Inc.; Karyopharm; and Samsung Bioepis. He is a stock shareholder (directly purchased) of Gilead Sciences, Inc.

Howard Bliwise, MD (peer reviewer) has no disclosures to report.

Mae Ochoa, RPh (peer reviewer) has no disclosures to report.

Poshala Tish Aluwihare, PhD (planning committee) has no disclosures to report.

Susan Perry (planning committee) has no disclosures to report.

Jan Perez (planning committee) has no disclosures to report.

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   (It's okay if you miss answering a question or get them wrong; you can still claim MOC)
2. Complete your post-test and evaluation at the conclusion of the webcast
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- Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation
- Complete the follow-up survey from CME Outfitters in approximately 3 months

CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity

CME for MIPS IMPROVEMENT ACTIVITY

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Chief, Division of Thoracic Medical Oncology
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David E. Gerber, MD

Professor of Internal Medicine and Population & Data Sciences
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Associate Director of Clinical Research
Harold C. Simmons Comprehensive Cancer Center at UT Southwestern
Dallas, TX

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Learning Objective 1

Apply molecular testing to identify predictive biomarkers for targeted therapy in advanced NSCLC.

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Learning Objective 2

Evaluate rationale for emerging therapies in advanced or metastatic NSCLC.

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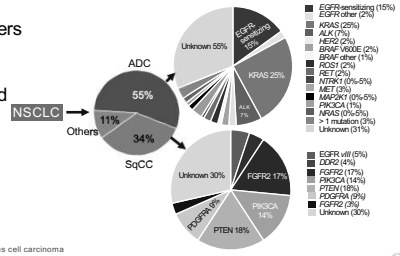
Learning Objective 3

Employ best practices to manage lung cancer during the COVID-19 pandemic.

Mutation Testing for Metastatic NSCLC

NSCLC: Complex Picture

- 85% of lung cancers
- Highly heterogeneous
- Majority presented in the advanced stage



ADC = adenocarcinoma; SqCC = squamous cell carcinoma

Li T, et al. *J Clin Oncol*. 2013;31(8):1039-1049.; Bubendorf L, et al. *Eur Respir Rev*. 2017;26(144):170007.; Zappa C, Mousa SA. *Transl Lung Cancer Res*. 2016;5(3):288-300. Brainard J, Farver C. *Mod Pathol*. 2019;32(1):16-26.

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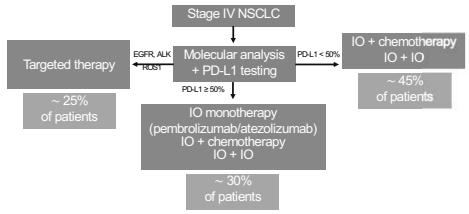
Advanced NSCLC: Biomarkers and Actionable Mutations

- EGFR
- ALK
- ROS
- BRAF V600
- MET exon 14
- NTRK
- RET
- HER2 (ERBB2)



Gregory LR. *J Natl Compr Canc Netw*. 2017;15(5S):686-688.; Kim SY, Halmos B. *Lung Cancer Manag*. 2020;9(3):LMT36.

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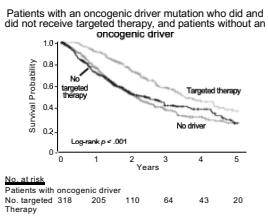
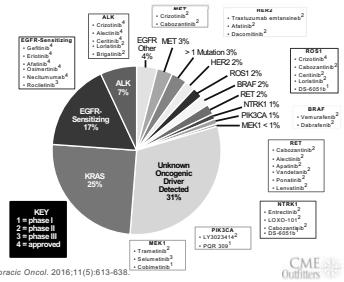
Targeting Actionable Mutations in NSCLC



No. at risk

Patients with oncogenic driver						
No. targeted Therapy	318	205	110	64	43	20
Targeted. therapy	260	225	143	72	36	23
Patients with no driver	360	250	122	59	36	23



Kris MG, et al. *JAMA*. 2014;311(19):1998-2006.; Tsao AS, et al. *J Thoracic Oncol*. 2016;11(5):613-638.

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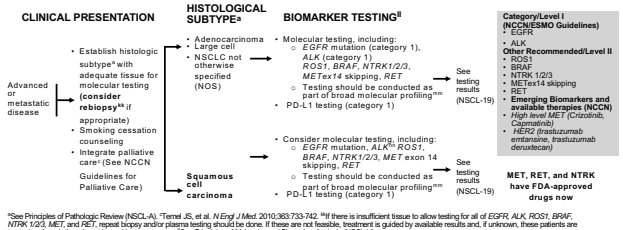
Current NCCN Guideline Testing Recommendations Include Testing for Many Gene Mutations



[a]See Principles of Pathologic Review (NSCL-A). [c]Temel JS, et al. *N Engl J Med*. 2010;363:733-742. [ll]If there is insufficient tissue to allow testing for all of *EGFR, ALK, ROS1, BRAF, NTRK 1/2/3, MET*, and *RET*, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes. [m]See Principles of Molecular and Biomarker Analysis (NSCL-H).
[mm]The NCCN NSCLC Guidelines Panel strongly advises broader molecular molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Biomarkers to Identify Patients for Therapies (NSCL-I). [hh]LAM VK, et al. *Clin Lung Cancer*. 2019;20:30-36.e3; Sands JM, et al. *Lung Cancer*. 2020;140:35-41.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ESMO = European Society for Medical Oncology; NCCN = National Comprehensive Cancer Network
Velcheti V, Pennell NA. *Ann Transl Med*. 2017;5(18):378.; National Comprehensive Cancer Network. NCCN. 2020. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.; Good Science Better Medicine Best Practice. ESMO. 2020. https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer.

Comparison of Molecular Assays for Biomarker Detection in NSCLC

Molecular Methods	Variant Types: Point Mutations	Small Deletion, Insertions	Copy Number Alterations	Rearrangements	Sensitivity (%)	Turnaround Time
Sizing assays	+/−	✓				2-3 days
PCR and Sanger sequencing	✓	✓			20-50	3-4 days
PCR and pyrosequencing	✓	+/−			20-50	3-4 days
PCR and mass spectrometry	✓	+/−			1-10	3-4 days
PCR and single-base extension	✓				1-10	3-4 days
qPCR and digital PCR	✓	✓		✓	.00001	2-3 days
Allele-specific PCR	✓					1-2 days
FISH			+/−	✓	< 1	2-3 days
NGS: targeted amplicon capture	✓	✓			1-10	7-10 days
NGS: targeted hybridization capture	✓	✓	✓	+/− 1	1-5	15-20 days
NGS: whole exome	✓	✓	✓	+/− 1	Variable	Weeks
NGS: whole genome	✓	✓	✓	✓	Variable	Weeks

FISH = fluorescent in situ hybridization; NGS = next-generation sequencing; PCR = polymerase chain reaction; qPCR = quantitative PCR
Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;(39):531-542.

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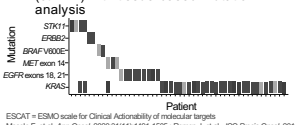
Detecting Genomic Alterations in Advanced NSCLC-NGS

- ESMO recommends using tumor multigene NGS in patients presenting with advanced non-squamous NSCLC
- NCCN recommends NGS testing be performed via a broad, panel-based approach, most typically performed by NGS, when feasible
- High concordance with liquid biopsy (ctDNA) with tissue-based mutation analysis



List of Genomic Alterations Level I/II/III According to ESCAT in Advanced Non-squamous

Gene	Alteration	Prevalence	ESCAT
EGFR	Common mutations (Del19, L858R) Acquired T790M exon 20 Uncommon *EGFR* mutations (G719X in exon 18, L861Q + S768I exon 20) Exon 20 insertions	15% (50%-60% Asian) 50% of *EGFR* mutant NSCLC 2%	IA IA IB IIB
ALK	Fusions (mutations as mechanism of resistance)	5%	IA
MET	Mutations exon 14 skipping Focal amplifications (acquired resistance on EGFR TKI in *EGFR*-mutant tumors)	3% 3%	IB IIB
BRAF V600E	Mutations	2%	IB
ROS1	Fusions (mutations as mechanism of resistance)	1%-2%	IB
NTRK	Fusions	0.23%-3%	IC
RET	Fusions	1%-2%	IC
KRAS[G12C]	Mutations	12%	IIB
ERBB2	Hotspot mutations Amplifications	2%-5%	IIB
BRCA 1/2	Mutations	1.2%	IIIA
PIK3CA	Hotspot mutations	1.2%-7%	IIIA
NRG1	Fusions	1.7%	IIIB

ESCAT = ESMO scale for Clinical Actionability of molecular targets
Mosele F, et al. *Ann Oncol*. 2020;31(11):1491-1505.; Remon J, et al. *JCO Precis Oncol*. 2019;3:PO.18.00211. ; NCCN. NSCLC v1.2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

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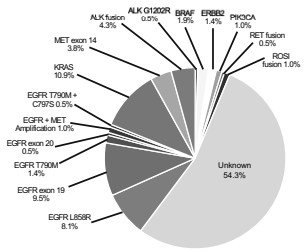
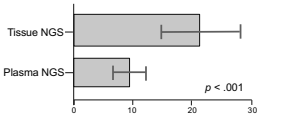
NSCLC Genetic Driver Mutation Identification by NGS



Genetic driver alteration identified by plasma next-generation sequencing (n = 210)

Tissue NGS	Plasma NGS
Slower turnaround time	Faster turnaround time
High concordance (89.6%)	Negative result is not confirmatory (60.6% concordance)

2 cases (-) in tissue NGS was (+) in plasma NGS



Turnaround time of plasma and tissue NGS; Plasma samples, n = 210; tissue samples, n = 107; The paired turnaround times were compared by a two-sided Wilcoxon signed-rank test

Sabari JK, et al. *J Natl Cancer Inst*. 2019;111(6):575-583.

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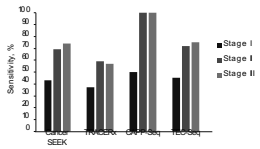
Evolving Role of NGS in NSCLC

- Potential to help manage NSCLC in all stages of cancer
- ctDNA sensitivity is low in early stages but high in advanced stages
- cfDNA capable of identifying all guideline genomic biomarkers



			cfDNA		Tissue
Guideline-Recommended Genomic Biomarkers (Selected)	TCGA	% of Total Cohort	Frequency of Alteration (%)	% of Total Cohort	Frequency of Alteration (%)
EGFR mutation	11.30%	15.20%	16.00%	14.20%	17.30%
ALK fusion	1.30%	2.10%	2.20%	3.20%	4.00%
ROS1 fusion	1.70%	0.00%	0.00%	0.70%	1.20%
BRAF mutation (V600E)	7.00%	0.70%	0.70%	0.70%	2.10%
RET fusion	0.90%	1.10%	1.10%	0.00%	0.00%
ERBB2 mutation	1.70%	1.10%	1.10%	0.40%	1.60%
MET exon 14 skipping variant	4.30%	3.50%	3.70%	1.80%	7.50%
MET amplification	2.20%	5.30%	5.60%	0.40%	1.60%
KRAS mutation	32.20%	31.60%	33.20%	8.50%	32.90%

Guibert N, et al. *Eur Respir Rev*. 2020;29(155):190052.; Leighl NB, et al. *Clin Cancer Res*. 2019;25(15):4691-4700.

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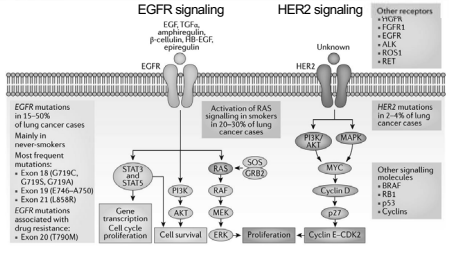
Receptor Signaling in NSCLC: Druggable Targets



Nature Reviews | Disease Primers

Mar N, et al. *Lung Cancer*. 2015;87(3):220-225.; Jebbink M, et al. *Cancer Treat Rev*. 2020;86:101996.

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HER2 in Lung Adenocarcinoma

- Protein overexpression (IHC 2+ or 3+) in 12%-20% of cases
- Amplification in ~ 3% of cases, around 10% of cases in EGFR TKI resistance
  - HER2 amplification and mutations usually do not occur together
- Activating mutations in ~ 2%-4% of cases
- How to define HER2-positive lung cancer?
- Which of them are suitable for treatment with anti-HER2 agents?

Li BT, et al. *J Thorac Oncol*. 2016;11(3):414-419.; Nakamura H, et al. *Int J Cancer*. 2003;103(1):61-66.; Yoshizawa A, et al. *Lung Cancer*. 2014;85(3):P373-P378.; Ekman S. *Ann Oncol*. 2019;30(3):P353-P355.

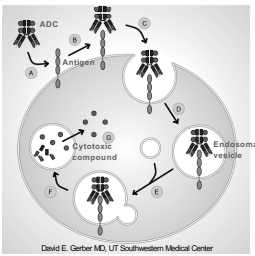
CME Outfitters

ADCs in NSCLC

Mechanism and Characteristics of ADCs in NSCLC

An Animated Tour

ADCs Deliver Lethal Payloads to the Target



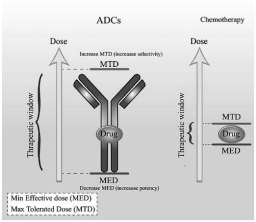
David E. Gerber MD, UT Southwestern Medical Center

A. Antigen access via circulation
B. Antigen binding
C. Antigen-ADC complex internalization
D. Incorporation into endosomal vesicles
E. Processing along endosomal-lysosomal pathway
F. Degradation in acidic and proteolytic rich environment
G. Intracellular release of cytotoxic compound

Parslow AC, et al. *Biomedicines*. 2016;4(3):14.

CME Outfitters

ADCs Can Extend the Therapeutic Window



Compared to conventional chemotherapy, ADCs can ↑ efficacy and ↓ toxicity:

- Targeted delivery of drugs to cancer cells → ↑ drug doses in tumor microenvironment → ↓ **minimum effective dose (MED)**
- Fewer drug molecules within normal, non-target tissues → ↑ **maximum tolerated dose (MTD)**

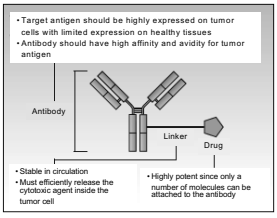
Nasiri H, et al. *J Cell Physiol*. 2018;233:6441-6457.

CME Outfitters

Tumor and ADC Characteristics Impact Efficacy and Toxicity

Tumor Characteristics

- Target antigen highly expressed on tumor
- Limited expression of target antigen on healthy tissues
- Target antigen not shed at high levels
- Target antigen-ADC complex internalized upon binding



ADC Characteristics

- Antibody has high affinity, avidity for target antigen
- Linker stable in circulation but efficiently releases payload inside tumor cell
- Highly potent drug

Thomas A, et al. *Lancet Oncol*. 2016;17(6):e254-e262.

CME Outfitters

Case Study: Meet Joanna

- Joanna is a 66-year-old woman with relapsed small cell lung cancer (SCLC) after platinum-etoposide and topotecan
- Treated with anti-DLL3 antibody-drug conjugate 4/2017-6/2017
- Excellent response to therapy but subsequent development of target-related toxicities of pleural, pericardial effusions

Select ADCs in NSCLC and Other Solid Tumors

Target	ADC	Tumors	Clinical Trial Number	Phase
Axl	BA3011 (CAB-AXL)	NSCLC, other solid tumors	NCT03425279	I, II
Axl	Enapotamab vedotin	NSCLC, other solid tumors	NCT02988817	I, II
B7-H3	MGC018	NSCLC, other solid tumors	NCT03729596	I, II
CD166	CX-2009	NSCLC, other solid tumors	NCT03149549	I, II
CD205/Ly75	MEN1309	Metastatic NSCLC, other solid tumors	NCT03403725	I
CD71	CX-2029	NSCLC, other solid tumors	NCT03543813	I, II
cMet	ABBV-399 (telisotuzumab vedotin)	NSCLC	NCT02099058, NCT03539536	I
cMet	SHR-A1403	NSCLC, other solid tumors	NCT03856541	I
cMet	TR1801	NSCLC, other solid tumors	NCT03859752	I
EGFR	AVID100	NSCLC, other solid tumors	NCT03094169	I, II
HER2	A166	Lung cancer, other HER2+ cancers	NCT03602079	I, II
HER2	DS-8201a	NSCLC, HER2 positive	NCT03505710, NCT02564900	II
HER2	FS-1502 (trastuzumab monomethyl auristatin F)	NSCLC, breast and other solid tumors	NCT03944499	I
HER2	SYD985 (trastuzumab vc-seco-DUBA)	NSCLC, other solid tumors	NCT02277717	I
HER2	XMT-1522	NSCLC, breast cancer	NCT02952729	I
HER3	U3 1402	NSCLC	NCT03260491	I
IGF-1R	W0101	NSCLC, other solid tumors	NCT03316638	I, II
mesothelin	BAY 94-9343 (anetumab ravtansine)	NSCLC, mesothelin positive, others	NCT01439152, NCT03455556	I
mesothelin	BMS-986148	NSCLC, other solid tumors	NCT02341625	I, II
ROR2	BA3021 (CAB-ROR2)	NSCLC, other solid tumors	NCT03504488	I, II
SLC34A2/NaPi2b	XMT1536	NSCLC, ovarian cancer	NCT03319628	I
Trop-2	IMMU-132 (sacituzumab govitecan)	SCLC, NSCLC, other epithelial cancers	NCT01631552	I, II

Deneka AY, et al. *Cancers*. 2019;11(9):1297.

CME Outfitters

ADCs Targeting Select Genomic Alterations in NSCLC

ADC	*Target*	*Phase (CT)*
Trastuzumab emtansine (T-DM1)	HER2	II (NCT02289833)
Trastuzumab emtansine (T-DM1)	HER2	II, in progress (NCT02675829)
Trastuzumab deruxtecan (DS-8201a)	HER2	I, in progress (NCT02564900)
Trastuzumab deruxtecan (DS-8201a)	HER2	II, in progress (NCT03505710)
U3-1402	HER3	I, in progress (NCT03260491)
Telisotuzumab vedotin (ABBV-399)	c-Met	I/Ib in progress (NCT02099058)
DS-1062	TROP2	I, in progress (NCT03401385)
Sacituzumab govitecan	TROP2	I (NCT01631552)

Payan S, et al. *Target Oncol*. 2020;15(4):429-448.

CME Outfitters

Trastuzumab Emtansine (T-DM1) in Previously Treated HER2 Metastatic NSCLC (NCT02289833)

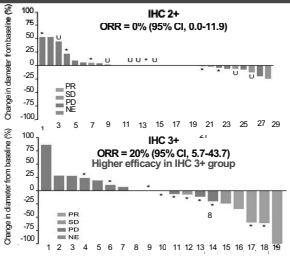
- Phase II
- Previously treated advanced HER-2 overexpressing (IHC 2+ or 3+)
- Age ≥ 18
- All patients received T-DM1 (3.6 mg/kg intravenously every 3 weeks)
- Median treatment duration was 3.6 months (0-24.8 months)

	T-DM1 (N = 49)
Any AE	45 (92%)
Serious AE	10 (20%)
Withdrawal due to AE	2 (4%)
Death as a result of AE	0
Death as a result of AE related to study drug	0

Peters S, et al. *Clin Cancer Res*. 2019;25(1):64-72.

CME Outfitters

Efficacy of T-DM1 in Previously Treated HER2 Metastatic NSCLC



Parameter	T-DM1 Patients with IHC 2+ (N = 29)	T-DM1 Patients with IHC 3+ (N = 20)
CR	0	0
PR	0	4 (20%)
SD	8 (28%)	4 (20%)
PD	16 (55%)	11 (55%)
DCR	8 (28%)	8 (40%)
ORR	0	4 (20%)
PFS	2.6 months	2.7 months

CR = complete remission ; PR = partial remission ; SD = stable disease ; PD = progressive disease; DCR = disease control rate; ORR = objective response rate ; PFS = progression free survival.
Peters S, et al. *Clin Cancer Res*. 2019;25(1):64-72.

CME Outfitters

T-DM1 in HER2-Mutant Lung Cancers (NCT02675829):Ongoing trial

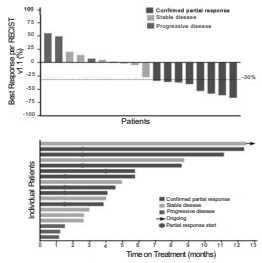
- Phase II basket trial
- Patients with metastatic lung adenocarcinoma
- Median age 64 (47-74)
- All patients received T-DM1 (3.6 mg/kg intravenously every 3 weeks
- Median treatment duration was 4 months

	T-DM1 (N = 18)
Any AE	YES Elevated AST, ALT (39%) Thrombocytopenia (33%)
Serious AE	YES Grade 3-4 anemia (6%)
Withdrawal due to AE	0
Death as a result of AE	0
Death as a result of AE related to study drug	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AE = adverse effect(s)
Li BT, et al. *J Clin Oncol*. 2018;36(24):2532-2537.

CME Outfitters

Efficacy of T-DM1 in HER2-Mutant Lung Cancers

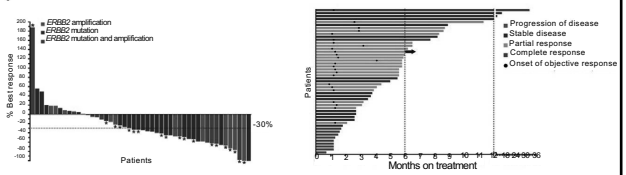


Parameter	T-DM1 (N = 18)
CR	0
PR	8 (44%)
SD	7 (39%)
PD	3 (17%)
DCR	15 (83%)
ORR	8 (44%)
PFS	5 months

Li BT, et al. *J Clin Oncol*. 2018;36(24):2532-2537.

Study Update: T-DM1 in HER2-Mutant and/or Amplified Lung Cancers (NCT02675829)

- N = 49 (including 18 from previous report)



Parameter	N = 49
ORR	25 (51%)
PFS	5 months

Similar ORR for both HER2 mutations and HER2 amplifications

Li BT, et al. *Cancer Discov*. 2020;10(5):674-687.

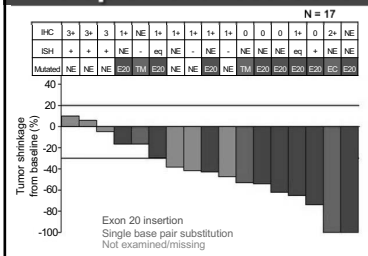
Trastuzumab deruxtecan(T-DXd) Targeting HER2 in Multiple Advanced Solid Tumors (NCT02564900):Ongoing Trial

- Phase I dose expansion in pre-treated HER-2 expressing (IHC≥ 1+) patients
- Median age 59
- Median treatment duration 10.6 months
- *HER2* mutation 61.2% (11/18)
- Most common *HER2* mutations among patients with NSCLC were exon 20 insertions 44.4% (8/18)
- Among the 18 patients with NSCLC, 27.8% (5/18) had received a prior HER2-targeted regimen, 22.2% (4/18) had received a prior EGFR inhibitor, and 5.6% (1/18) had received a prior anaplastic lymphoma kinase inhibitor

	T-DXd (DS-8201) (N = 18) NSCLC
Any AE	18 (100%)
Serious AE related to study drug	2 (11.2%)
Withdrawal due to AE	NR
Death as a result of AE	1 (5.6%)
Death as a result of AE related to study drug	1 (5.6%)

Tsurutani J, et al. *Cancer Discov*. 2020;10(5):688-701.

Efficacy of T-DXd Targeting HER2 in Multiple Advanced Solid Tumors



Parameter	T-DXd (DS-8201) All Patients (N = 18)	T-DXd (DS-8201) Patients with HER-2 Mutant NSCLC (N = 11)
CR	0	0
PR	10 (55.6%)	8 (72.7%)
SD	4 (22.2%)	2 (18.2%)
PD	3 (16.7%)	1 (9.1%)
DCR	14 (77.8%)	10 (90.9%)
ORR	10 (55.6%)	8 (72.7%)
PFS	11.3 months	

Tsurutani J, et al. *Cancer Discov*. 2020;10(5):688-701.

CME Outfitters

T-DXd in HER2-Mutatated Metastatic NSCLC (DESTINY-Lung01) (NCT03505710): Ongoing Trial

- Phase II in patients with non-squamous NSCLC with HER2-overexpressing or HER2-activating mutants
- Median age 63 (34-83)
- 6.4 mg/kg every 3 weeks
- Median treatment duration 7.75 months
- Data presented for HER-2 mutated group
- Most common *HER2* mutations in the kinase domain (90.5%)
- Most patients (90.5%) had prior platinum-based therapy and 54.8% had anti PD-1 or PD-L1 treatment

	T-DXd (DS-8201) (N = 42)
Any AE	42 (100%)
Serious AE related to study drug	22 (52.4%)
Withdrawal due to AE	10 (23.8%)
Death as a result of AE	0
Death as a result of AE related to study drug	0

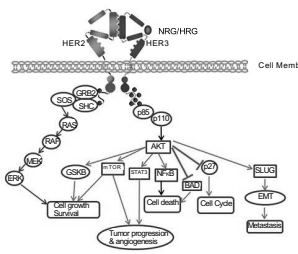
Parameter	N = 42
ORR	61.9%
PFS	14 months

Smit EF, et al. *J Clin Oncol*. 2020;38(suppl).Abstract No. 9504.

CME Outfitters

HER3 targeting ADCs in NSCLC

- HER3 (ERBB3) is a member of the EGFR family
- Dimerizes with HER2 to activate oncogene signalling via PI3K/AKT, MAPK and JAK/STAT pathways
- HER3 activation leads to treatment failure
- Target for ADCs in multiple malignancies



Mishra R, et al. *Oncol Rev*. 2018;12(1):355.

CME Outfitters

Patritumab Deruxtecan (U3-1402) Targeting HER3 in EGFR-Mutated NSCLC (NCT03260491): Ongoing Trial

- Phase I dose escalation and dose expansion in advanced EGFRm NSCLC after failure of EGFR TKI and platinum-based chemotherapy
- Age ≥ 18 (United States) or ≥ 20 (Japan)
- Median treatment cycles 3 (1-19)
- 28 patients continuing at data cutoff

	Patritumab Deruxtecan (U3-1402) (N = 56)
Any AE	YES
Serious AE related to study drug	YES Thrombocytopenia 25% Neutropenia 16%
Withdrawal due to AE	0
Death as a result of AE	0
Death as a result of AE related to study drug	0

Yu HA, et al. *Ann Oncol*. 2020;31(Suppl 4):S1189-S1190.

CME Outfitters

Efficacy of U3-1402 Targeting HER3 in EGFR-Mutated NSCLC: Ongoing Trial

- 5.6 mg/kg
- 22/56 (39%) patients had best percentage decrease in sum of tumor diameters ≥ 30%
- Efficacy was observed in patients with several mechanisms of resistance including EGFR, C797S, MET amp, HER2m, BRAF fusion, and PIK3CAm

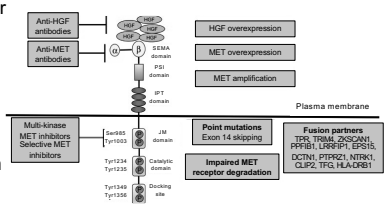
Parameter	Patritumab Deruxtecan (U3-1402) (N = 56)
CR	1 (2%)
PR	13 (23%)
SD	25 (45%)
PD	9 (16%)
DCR	39 (70%)
ORR	14 (25%)

Yu HA, et al. *Ann Oncol*. 2020;31(Suppl 4):S1189-S1190.

CME Outfitters

c-MET targeting ADCs in NSCLC

- c-MET is a HGF receptor
- Activation leads to excessive cell proliferation via multiple pathways including PI3K/AKT, RAS/ERK/MAPK and Wnt/β-catenin
- Overexpression/mutation of c-MET in NSCLC may lead to tumor invasion and metastasis



Liang H, Wang M. *Onco Targets Ther*. 2020;13:2491-2510.

CME Outfitters

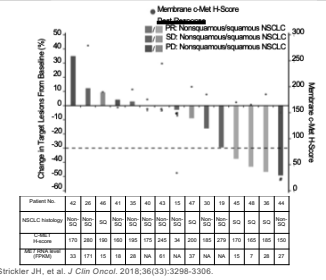
Telisotuzumab Vedotin (ABBV-399/Teliso-V) Targeting c-Met in Patients with Advanced Solid Tumors (NCT02099058):Ongoing trial

- Phase I dose escalation study in advanced solid tumors including NSCLC
- NSCLC with c-MET + IHC H-score ≥ 150)
- 0.15 mg to 3.3 mg/kg
- IV dosing every 3 weeks

	ABBV-399/Teliso-V (N = 48) NSCLC (N = 16)
Any AE	46 (96%)
Serious AE related to study drug	2 (4%)
Withdrawal due to AE	11 (22.9%)
Death as a result of AE	4(8%)
Death as a result of AE related to study drug	0 (0)

Strickler JH, et al. *J Clin Oncol*. 2018;36(33):3298-3306.

Efficacy of ABBV-399 Targeting c-Met in Patients with Advanced Solid Tumors

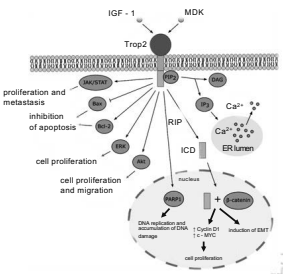


Parameter	ABBV-399/Teliso-V Patients with cMet-Positive NSCLC (N = 16)
CR	0
PR	3 (18.8%)
SD	6 (37.5%)
PD	5 (31.3%)
DCR	9 (56.3%)
ORR	18.8 %
PFS	5.7 months

Strickler JH, et al. *J Clin Oncol*. 2018;36(33):3298-3306.

Trophoblast Cell-Surface Antigen 2(TROP2) targeting ADCs in NSCLC

- TROP2 is a glycoprotein which mediates cell proliferation, growth and calcium mobilization via a complex network of signalling pathways
- Overexpression correlates with poor prognosis in some malignancies including NSCLC



Lenárt S, et al. *Cancers (Basel)*. 2020;12(11):E3328.

DS-1062 in Targeting TROP2 in Advanced NSCLC (NCT03401385): Ongoing Trial

- Phase I dose escalation and dose expansion with unresectable NSCLC refractory to/relapsed from standard treatment with measurable disease (RECIST v1.1) and available tumor for retrospective TROP2 evaluation were eligible
- Age ≥ 18 (United States) or ≥ 20 (Japan)
- Median treatment cycles 3 (1-19)
- Treatment was well tolerated up to 8 mg/kg, and a dose effect on antitumor activity was observed over 2.0-10.0 mg/kg in heavily pretreated patients with prior progression on standard treatment

	(DS-1062) (N = 95)
Any AE	91 (96%)
Serious AE related to study drug	17 (18%)
Withdrawal due to AE	NR
Death as a result of AE	0
Death as a result of AE related to study drug	0

Parameter	N = 88 (response-evaluable)
PR	22 (25%)

Lisberg AE, et al. *J Clin Oncol*. 2020;38(suppl). Abstract No. 9619.

CME Outfitters

Sacituzumab Govitecan (IMMU-132) Targeting Trophoblast Cell-Surface Antigen 2 (TROP2) in Advanced NSCLC (NCT01631552)

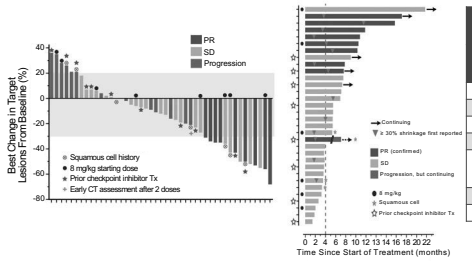
- Pretreated patients with metastatic NSCLC
- Median age 64 (40-68)
- Not preselected on the basis of TROP-2 expression on their tumors
- TROP-2 is not a predictive biomarker for response

	Sacituzumab Govitecan (IMMU-132) (N = 54)
Any AE	YES
Serious AE related to study drug	YES Neutropenia 28% Leukopenia 9% Pneumonia 9% Diarrhea 7%
Withdrawal due to AE	2 (3.7%)
Death as a result of AE	0
Death as a result of AE related to study drug	0

Heist RS, et al. *J Clin Oncol*. 2017;35(24):2790-2797.

CME Outfitters

Efficacy of IMMU-132 Targeting TROP2 in Advanced NSCLC



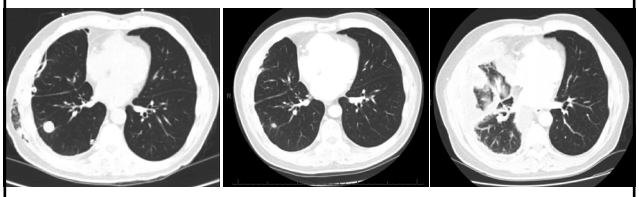
Parameter	Sacituzumab Govitecan (IMMU-132) Evaluable Patients (N = 47)
CR	0
PR	9 (19%)
SD	23 (49)
PD	15 (32%)
DCR (PR + SD ≥ 4 months)	20 (43%)
ORR	9 (19%)
PFS	5.2 months

Heist RS, et al. *J Clin Oncol*. 2017;35(24):2790-2797.

Cancer Care During COVID-19

Case Study: Meet Frank

- 63-year-old man with mesothelioma
- Received cisplatin-pemetrexed pre-op chemotherapy 12/2019-2/2020 with excellent response
- Offered surgery 3/2020 but chose to delay due to COVID concern
- Returned to clinic 8/2020, with imaging showing profound growth in tumor, now unresectable
- Chemotherapy restarted with hope to render resectable again



December 2019 March 2020 August 2020

Impact of COVID-19 on Clinical Trials

FDA Guidance (updated September 21, 2020)

- Purpose: Protect trial participants and manage study conduct
- Recognized challenges: Quarantines, site closures, travel limitations, interruptions to supply chain of investigational product, or possibility of staff/patients becoming infected with COVID-19
- Thus, difficulties meeting protocol-specified procedures (administering treatment; adhering to protocol-mandated visits, lab tests, imaging studies
- Consider: Telephone or video visits; local (i.e., near patient's home) lab and imaging studies; delaying some assessments; alternative sites for treatment administration; remote monitoring
- *Remains in effect only during the COVID-19–related public health emergency*

U.S. Food and Drug Administration (FDA) Website. 2020. https://www.fda.gov/media/136238/download.

CME Outfitters

Impact of COVID-19 on Clinical Trials

NIH Central IRB (CIRB) Guidance

- Clinical evaluations, blood tests, radiology studies, administration of non-investigational study treatments may be administered by non-study local healthcare providers
- Can obtain informed consent remotely
- Can use electronic signatures

NCI Cancer Therapy Evaluation Program (CTEP) Guidance

- "Virtual" or "telemedicine" visits may be used
- Protocol-required laboratory/imaging tests and treatment may be delayed
- Local healthcare providers may perform study follow-up
- May ship oral study therapy directly to patients' homes

National Cancer Institute (NCI) Central Institutional Review Board. NCI Website. 2020. https://www.ncicirb.org/announcements/frequently-asked-questions-regarding-covid-19-and-cirb. Department of Health & Human Services.; Cancer Therapy Evaluation Program (CTEP) Website. 2020. https://ctep.cancer.gov/content/docs/Memorandum_on_Interim_Guidance_for_Clinical_Trial_Activities_Affected_by_the_Novel_Coronavirus-3-13-2020.pdf.

CME Outfitters

ASCO Guidelines for Clinical Trials

- Manage current patients based on sponsor policies and in accord with agency guidance
- Continue treatment on protocol, if possible, maintaining good clinical practice
- Consult sponsor and IRB (Institutional Review Board) with inquiries regarding deviations from protocol requirements during pandemic
- Protocol monitoring modifications may include all study monitoring being virtual visits if the trial sponsor agrees
- Ensure access to drugs prior to patient visit scheduling
- Resume screening and enrollment with consideration to COVID-19 exposure; testing may be appropriate
- Expand access to clinical trial enrollment as imaging, surgery, and ability to collect biospecimens expand safely for patients and staff
- Consider discussion with sponsor regarding eliminating nonessential tests needed for study enrollment and remote laboratory testing
- Contact Principal Investigator and/or trial sponsor to discuss anticipated protocol deviations during the pandemic

ASCO. American Society of Clinical Oncology. 2020. https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf.

CME Outfitters

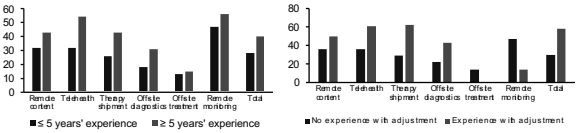
Clinical Trials in LC During COVID-19

- Enrollment for clinical trials have dropped significantly

Changes in enrollment by patient and trial characteristics and by spread of COVID-19

Characteristic	No./total No. (%)			OR (95%CI)	*P* value
	All enrolled patients	Patients enrolled weeks 1-11	Patients enrolled weeks 12-17		
Research setting					
Treatment	1316/1870 (70.4)	948/1431 (66.2)	368/439 (83.8)	1 [Reference]	NA
Cancer control and prevention	554/1870 (29.6)	483/1431 (33.8)	71/439 (16.2)	0.38 (0.29-0.50)	< .001

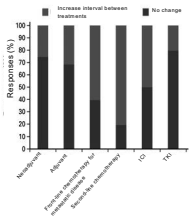
- Clinical research professional's perception on clinical trial adjustment is dependent on experience

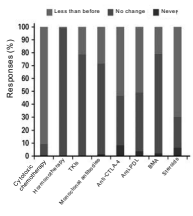


Unger JM, et al. *JAMA Network Open*. 2020;3(6):e2010651.; Gerber DE, Sheffield TY. *JNCCN*. 2020;1-8.

Impact of COVID-19 on Oncology Practice

- Effect of COVID-19 on treatment decisions
  - Definitely (61%)
  - Probably/Possibly (36%)
  - Probably/Definitely not (4%)
- Factors affecting systemic therapy
  - Age of patient (81%)
  - Comorbidities (92%)
- Use of G-CSF
  - Increased 78%
  - No change 22%
- Telemedicine usage
  - Yes 80%





BMA = bone-modifying agents; ICI = immune checkpoint inhibitor; I KI = tyrosine kinase inhibitor
Ürün Y, et al. *JCO Global Oncol*. 2020(6):1248-1257.

TERAVOLT: Assessing Thoracic Cancer Patients with COVID-19

- Initial data from a cohort of 200
- 152 (76%) patients were hospitalized and 66 (33%) died
- Death was mainly due to COVID-19 complications
- Anti-cancer treatment did not affect fatality
- 151 (76%) patients with NSCLC

Factors Associated with Death

	Odds Ratio (95% CI)
COPD	1.18 (0.59-2.37)
Hypertension	1.16 (0.61-2.21)
Female sex (vs. male)	0.69 (0.33-1.44)
Age > 65 (vs. ≤ 65)	1.53 (0.77-3.03)
Current or former smoker (vs. never smoker)	3.18 (1.11-9.06)
Outcome includes death during hospitalization, in the intensive care unit, or at home	

Garassino MC, et al. *Lancet Oncol*. 2020;21(7):914-922.

Treating NSCLC During COVID-19: Medical Oncology

Stages I/II	Stage III	Stage IV
Neoadjuvant chemotherapy (enabling deferral of surgery by 3 months) in clinical stage II	Stage III NSCLC should receive high priority	Consider all available treatment options for newly diagnosed metastatic NSCLC
Role of adjuvant chemotherapy at the present time should be reconsidered	Guaranteeing subsequent use of durvalumab within 42 days after CT/RT completion	ICI schedule modified/delayed to reduce clinical visit, using 4-weekly nivolumab 480 mg or 6-weekly pembrolizumab 400 mg instead of the standard 2-weekly or 3-weekly
Use of granulocyte growth factors in adjuvant or neoadjuvant platinum-based chemotherapy	Use of granulocyte growth factors in high febrile neutropenia risk (10%-15%)	TKIs in oncogene-driven NSCLC must continue unaltered

Passaro A, et al. *ESMO Open*. 2020;5(Suppl 3):e000820.

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Management Strategies for NSCLC During COVID-19

Management Recommendations and Additional Considerations for Patients With NSCLC by Stage of Disease

Stage	Recommendation	Additional Consideration
I	Defer surgery for lung nodules < 2 cm, GGOs, carcinoid tumors	Consider SBRT/ablation
	Follow ACS guidelines; decisions must be based on institutional resources	
II/III	Delay adjuvant chemotherapy 3-4 months postoperatively	Consider withholding adjuvant chemotherapy for patients age > 75 years or with significant comorbidities
		Consider neoadjuvant/induction therapy if surgery not immediately feasible
III	Delay start of consolidation durvalumab up to 6 weeks from completion of concurrent chemoradiotherapy	Consider delaying start of concurrent chemoradiotherapy on case-by-case basis; discuss with radiation oncology the possibility of sequential chemotherapy followed by concurrent chemoradiotherapy
	Hypofractionated radiotherapy schedules should be used with concurrent chemotherapy, when feasible	
	No consolidation chemotherapy should be administered after completion of concurrent chemoradiotherapy	Consider using once-every-3-week chemotherapy regimens, instead of weekly chemotherapy, to minimize exposure
IV	After initial induction chemoimmunotherapy, considerations should be made to space intervals between maintenance infusions, especially for those who have been receiving therapy for > 6 months and those with excellent clinical/radiographic response	In patients receiving TKIs, do not routinely hold TKIs for COVID-19 – positive patients unless symptomatic
	Stop immunotherapy for patients who have completed 2 years of treatment	If patients are symptomatic and there is concern for pneumonitis, advise testing for COVID-19 before making decision about stopping therapy

ACS = American College of Surgeons; GGO = ground-glass opacity; SBRT = stereotactic body radiotherapy
Singh AP, et al. *JCO Oncol Pract*. 2020;16(9):579-586.

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Use of Telemedicine in Patients with Lung Cancer

- Worldwide backlog of surgeries due to COVID-19
- Significant upsurge in the use of telemedicine
- ESMO recommendations for use of telemedicine in patients with lung cancer
  - All non-priority patient appointments
  - Non-urgent situations for established patients without new complaints
  - Patients on long-term follow-up with low/intermediate risk of relapse
- ASCO also has detailed guidelines for use of telemedicine in cancer care

McCall B. *The Lancet Digital Health*. 2020;2(9):e456-e457.; Passaro A, et al. *ESMO Open*. 2020;5(Suppl 3):e000820.; ASCO Website. 2020. https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf.

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Discussion Points

- How has COVID-19 impacted your practice?
- How do you convey prognosis?
- How do you explain disease progression when you cannot share scanned images?

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely

- Apply predictive biomarkers to determine appropriate treatment
- Utilize liquid biopsy and NGS for molecular diagnosis
- Evaluate complexities, challenges, and potential of ADCs for NSCLC
- Modify treatment plans to deliver cancer care during the COVID-19 pandemic

To Ask a Question

Please click on the *Ask Question* tab and type your question. Please include the faculty member's name if the question is specifically for him/her.

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AFTER THE SHOW

Questions & Answers

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Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation so we can submit your credit to ABIM.

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- Complete the follow-up survey from CME Outfitters in approximately 3 months

CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity

CME for MIPS IMPROVEMENT ACTIVITY

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TV-121-120120-65

Attendance Form for Groups

Please complete and FAX to **614.929.3600**

Activity Title and Faculty:

The Role of Antibody Drug Conjugates in Advanced Non-Small Cell Lung Cancer: Guidance for Today and the Path Forward

with Hossein Borghaei, DO, MS (Moderator); Enriqueta Felip, MD, PhD; and David E. Gerber, MD

Site/Institution Name: ____________________

Practice Setting: ❑ Office-Based ❑ Hospital ❑ Clinic ❑ Managed Care ❑ Small Group Practice (less than 5) ❑ Large Group Practice (more than 5) ❑ Other: ____________________

Address: ____________________

City: ____________________ State: ________ ZIP: ____________

Site Coordinator: ____________________ Phone: ____________________

Fax: ____________________ Email: ____________________

Completion Date: ____________ We participated in: ____________________

Attendee Name (please print)	Please Circle Discipline						
____________________	MD	DO	PA	NP	RN	Pharm	Other: ____________
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____________________	MD	DO	PA	NP	RN	Pharm	Other: ____________

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